bjh research paper

Life expectancy of follicular lymphoma patients in complete response at 30 months is similar to that of the Spanish general population

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Summary

The use of immunochemotherapy has improved the outcome of follicular lymphoma (FL). Recently, complete response at 30 months (CR30) has been suggested as a surrogate for progression-free survival. This study aimed to analyse the life expectancy of FL patients according to their status at 30 months from the start of treatment in comparison with the sex and age-matched Spanish general population (relative survival; RS). The training series comprised 263 patients consecutively diagnosed with FL in a 10-year period who needed therapy and were treated with rituximab-containing regimens. An independent cohort of 693 FL patients from the Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO) group was used for validation. In the training cohort, 188 patients were in CR30, with a 10-year overall survival (OS) of 53% and 87% for non-CR30 and CR30 patients, respectively. Ten-year RS was 73% and 100%, showing no decrease in life expectancy for CR30 patients. Multivariate analysis indicated that the FL International Prognostic Index was the most important variable predicting OS in the CR30 group. The impact of CR30 status on RS was validated in the independent GELTAMO series. In conclusion, FL patients treated with immunochemotherapy who were in CR at 30 months showed similar survival to a sex- and age-matched Spanish general population.

Keywords: follicular lymphoma, complete response, survival.

First published online 22 February 2019
doi: 10.1111/bjh.15805

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Received 14 September 2018; accepted for publication 21 December 2018
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Follicular lymphoma (FL) is the most prevalent indolent lymphoma in Western countries and is characterized by its responsiveness to therapy followed by repeated relapses. The use of immunochemotherapy, including rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) (Hiddemann *et al*, 2005; Federico *et al*, 2013), cyclophosphamide, vincristine and prednisone (R-CVP) (Marcus *et al*, 2005), fludarabine and mitoxantrone (R-FM) (Federico *et al*, 2013) or bendamustine (R-B) (Rummel *et al*, 2013; Flinn *et al*, 2014) has allowed high complete response (CR) rates with substantial advances in progression-free survival (PFS) and overall survival (OS). Thus, the median OS has improved, from about 10 years to 15 or 20 years (Liu *et al*, 2006; Sacchi *et al*, 2007; Junlén *et al*, 2015; Provencio *et al*, 2017a). Nevertheless, FL remains largely incurable and most patients eventually relapse/progress, including approximately 20% during the maintenance period (Salles *et al*, 2011). Recently, Casulo *et al* (2015) studied 588 FL patients from the National LymphoCare Study (NLCS) treated with R-CHOP as first-line therapy and observed that those patients who experience early progression of disease (within 2 years of first-line therapy) had a substantially higher risk of death. On the contrary, those patients reaching CR and maintaining this response for years are considered to have a good prognosis. In this sense, CR at 30 months (CR30) after initiation of induction therapy is considered a good surrogate for PFS (Shi *et al*, 2017) and, possibly OS. More recently, CR30 after autologous stem cell transplantation (ASCT) in FL patients was also described as surrogate for OS (Jiménez-Ubieto *et al*, 2017).

New treatment approaches are currently available for patients with FL in relapse/progression, including new immunotherapies and small molecules with targeted therapy. Many of these drugs have shown to be very active against the disease, but have also shown significant toxicities (Radford *et al*, 2013; Cheah *et al*, 2015; Salles *et al*, 2017). Therefore, it is crucial to select the best candidates for these new therapies, namely those with poor life expectancy due to disease.

In this setting, this study aimed to analyse the life expectancy of patients with FL according to response assessed at 30 months from the start of treatment and compare it with that of the sex and age-matched Spanish general population.

Patients and methods

Patients

Two hundred and sixty-three patients (median age, 59 years; female/male, 142/121) consecutively diagnosed with FL grades 1, 2 and 3a in two associated centres between January 2004 and January 2014 were retrospectively enrolled in the present study as the training cohort.

The only criterion for inclusion in the study was the need for treatment according to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (Brice *et al*, 1997). Fifty-six patients diagnosed in the same time period and followed with a watchful waiting policy were not included in the series. Another 19 patients diagnosed in the same time period and followed with a watchful waiting policy, but eventually needed therapy were included in the analysis from the time of treatment. Patients diagnosed with FL grade 3b, primary cutaneous follicle centre lymphoma, and FL with component of diffuse large B-cell lymphoma (DLBCL) were not included in the study. The training series was used to explore the impact of CR30 on the OS and to fully characterize CR30 patients in a homogeneous series, with complete clinico-biological data and treated according to well-defined institutional guidelines. Main initial features of the patients are described in Table I. Median age was 59 years (range, 26–86) and the male/female distribution was 142/121. The histological distribution was as follows: FL grade 1, 24%; FL grade 2, 47%; FL grade 3a, 18%; the grade could not be determined in 28 patients (11%). Thirty-three percent of patients had a high-risk FL International Prognostic Index (FLIPI) score. Treatment slightly varied over time and was R-CHOP/R-FCM (rituximab, fludarabine, cyclophosphamide and mitoxantrone) in 70% of the patients. Eighty-eight patients (34%) received maintenance with rituximab. All the patients gave informed consent to participate in the study according to the declaration of Helsinki and the ethical standards of the Ethic Committee of the Hospital Clínic de Barcelona and in each participating centre in accordance with institutional standards.

An independent series of 693 patients (median age, 58 years; female/male, 380/313) diagnosed with FL grades 1, 2 and 3a in the same period of time throughout 19 Spanish hospitals from the Spanish group of lymphoma and autologous stem-cell transplantation (Grupo Español de Linfomas y Trasplante Autólogo de Médula Óse; GELTAMO) were retrospectively included in this study as a validation cohort. Main features of this series are described in Table I. PFS and OS of the training and validation series are shown in Fig 1.

Table I. Main initial features, treatment and outcome of patients from training and validation cohorts.

Characteristics	Training cohort (n = 263)	Validation cohort (n = 693)
Age >60 years	119 (45%)	305 (44%)
Sex (Female/Male)	142/121	380/313
Histological grade		
Grade 1/2	187 (71%)	520 (75%)
Grade 3a	48 (18%)	115 (17%)
Undetermined	28 (11%)	58 (8%)
Bulky disease	63 (24%)	–
Stage III–IV disease	201 (76%)	536 (78%)
High serum LDH	59 (22%)	NA
High serum β2 m	123 (47%)	173 (31%)
FLIPI		
Low risk	68 (26%)	153 (30%)
Intermediate risk	95 (36%)	163 (31%)
High risk	86 (33%)	203 (39%)
Treatment		
R-CHOP	161 (61%)	376 (54%)
R-FCM	24 (9%)	68 (10%)
R-CVP	36 (14%)	72 (10%)
Others	32 (16%)	177 (26%)
Maintenance with rituximab	88 (33%)	163 (28%)
Response after induction therapy		
CR/CRu	210 (80%)	525 (76%)
PR	44 (17%)	145 (21%)
Failure	9 (3%)	23 (3%)
PFS at 5 years (95% CI)	63% (57–69%)	64% (60–68%)
OS at 5 years (95% CI)	87% (83–91%)	84% (81–87%)

β2 m, β2-microglobulin; CI, confidence interval; CR, complete response; CRu complete response unconfirmed; FLIPI, Follicular Lymphoma International Prognostic Index. LDH, lactate dehydrogenase; NA, not available; OS, overall survival; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone); R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-FCM, rituximab, fludarabine, cyclophosphamide and mitoxantrone.

Assessment of response and outcome

Response to treatment, relapse, survival and causes of death were collected. Response was assessed according to conventional criteria based on computed tomography (CT) scans (Cheson *et al*, 1999). A new bone marrow biopsy was mandatory in cases with bone marrow involvement before treatment. CR was defined as the total disappearance of tumour masses and disease-related symptoms as well as the normalization of the initial abnormal tests for at least 1 month. Complete remission unconfirmed (CRu) was considered when tumour mass or organ infiltration decreased by more than 75% along with the disappearance of disease-related symptoms but with residual masses >1·5 cm. Partial response (PR) was considered when tumour mass or organ infiltration decreased by at least 50% along with the disappearance of disease-related symptoms.

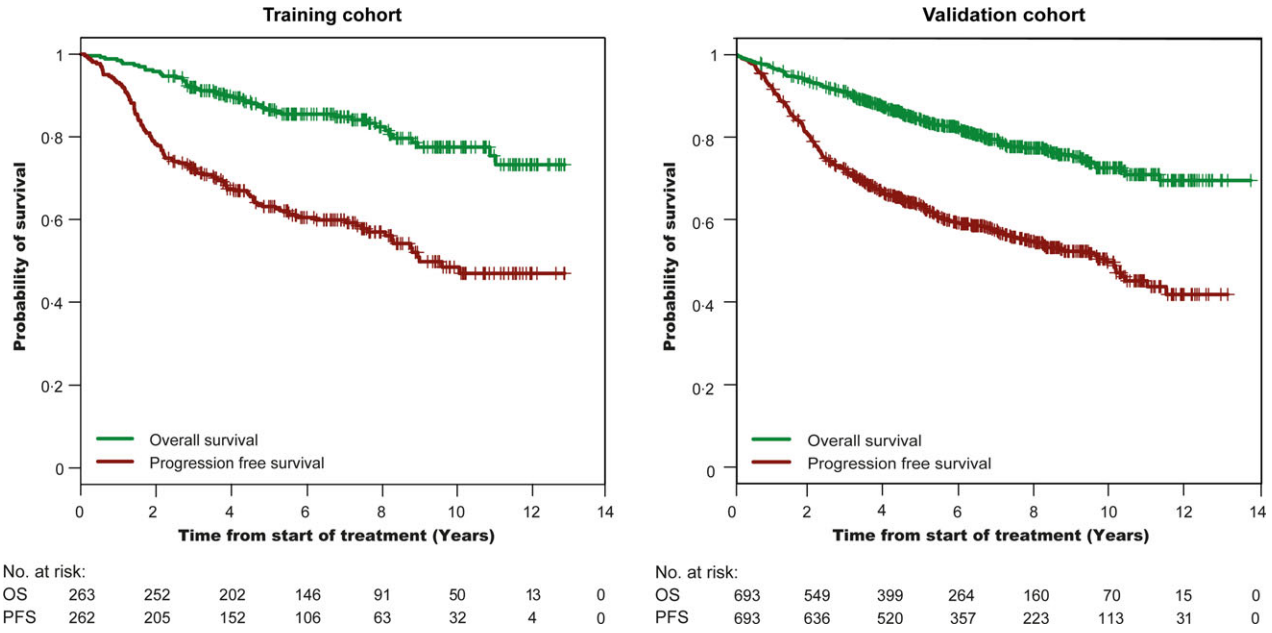

Fig 1. Progression-free survival (PFS) and overall survival (OS) of the training and validation cohorts.

In addition, in 158 patients of the training series (60%), fluorodeoxyglucose-positron emission tomography (PET)/CT scan was available at the end of induction treatment. In these cases, we also analysed response as assessed by PET/CT scan according to the current criteria (Cheson *et al*, 2007, 2014). Thus, patients with residual masses were considered in PR when PET scan was positive and in CR when PET scan was negative (Cheson *et al*, 2007). Patients not included in these categories and early deaths were considered as non-responders. Disease relapse or progression was defined as the appearance of new symptoms or signs of the disease as demonstrated by lymph node biopsy or other appropriate studies. PFS and OS were calculated according to standard definitions (Cheson *et al*, 2007). A retrospective review of all imaging studies in the training series (both after the induction and at 30 months) was carried out.

CR30 definition

Complete response assessed by CT scan at 30 months (CR30) from start of therapy was established as the main end point of the study. The 30 months cut-off point was selected based on the duration of induction therapy with 24-months maintenance treatment in addition, as well as data from previous reports (Casulo *et al*, 2015; Shi *et al*, 2017). CR30 included those patients who reached CR during induction and maintained the status at 30 months, as well as those in partial response (PR) after induction who reached CR during the maintenance period.

Statistical analysis

Differences among the subgroups of patients were assessed by using the Chi-square test (two-tailed), the Student's *t* test or nonparametric tests whenever necessary. The actuarial survival analysis was performed by the Kaplan and Meier method and differences assessed by the log-rank test. To evaluate the prognostic impact of different variables in PFS and OS, multivariate analyses were performed with the stepwise proportional hazards model (Cox model). $P < 0{\cdot}05$ were considered statistically significant. A "land-mark" at 30 months from start of therapy was established to assess survival. Finally, relative survival (RS) was analysed with respect to a sex- and age-matched Spanish population (www.mortality.org) using *R* software, version 3.3.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Relative survival is a net survival measure representing cancer survival in the absence of other causes of death, and is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer-free individuals. The formulation is based on the assumption of independent competing causes of death (Sasieni & Brentnall, 2017).

Results

Response to therapy, CR30 and outcome

After induction therapy, 160 patients (61%) achieved CR, 50 (19%) CRu, 44 (17%) PR and 9 (3%) showed treatment failure. After a median follow-up of 7 years (range: 2·3–

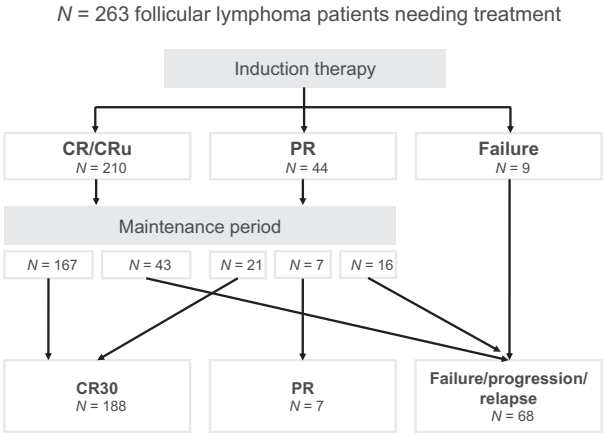

Fig 2. Patient's disposition as evaluated by computed tomography scan. CR, complete response; CR30, complete response at 30 months; CRu, complete response unconfirmed; PR, partial response.

12·9 years) for surviving patients, 98 patients (37%) experienced relapse/progression with a 5- and 10-year PFS of 63% [95% confidence interval (CI): 57–69%] and 49% (95% CI: 41–57%), respectively. During the follow-up before 30 months, 59 patients (43 in CR/CRu and 16 in PR) eventually progressed, whereas 21 PR patients achieved CR. Thus, at 30 months, 188 patients were in CR (CR30), 7 in PR and 68 had progressed. Fourteen patients died before this point. The patient disposition is shown in Fig 2.

CR30 patients more frequently presented with early stage, no extranodal involvement, no bulky disease, no bone marrow infiltration, normal serum β2-microglobulin (β2 m) and low-risk FLIPI compared to the remaining patients (Table II). Therapy administered did not influence CR30 status. In addition, as expected, maintenance with rituximab was related to a higher probability of CR30. PET/CT scan was available at the end of induction treatment in 158 patients: 116 (73%) were in complete metabolic response, 35 (22%) in partial metabolic response and 7 (5%) showed disease progression.

Forty-six patients died during follow-up with a 5- and 10-year OS of 87% (95% CI: 83–91%) and 78% (95% CI: 72–84%), respectively. Initial variables predicting shorter OS were older age (>60 years), poor performance status [Eastern Cooperative Oncology Group (ECOG) > 1], extranodal involvement, high serum lactate dehydrogenase (LDH), high serum β2 m, and high risk FLIPI ($P < 0{\cdot}03$ in all cases).

OS and life expectancy in CR30 patients

Thirty-one of the 188 CR30 patientseventually relapsed and 21 patients were re-biopsied at that point: FL grades 1–2, 67%, FL grade 3a, 11% and DLBCL, 22%. In two patients a fine needle aspirate was performed. Most patients (87%) received salvage treatment with immunochemotherapy, including R-CHOP, R-B and R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin), or rituximab monotherapy, whereas a watchful waiting policy was adopted in 13%. After salvage treatment, 70% of patients achieved CR/CRu. 5-year PFS from relapse was 65% (95% CI: 47–83%). Thirteen patients died during the follow-up. The causes of death were progression ($n = 3$), second malignancies ($n = 4$), cardiovascular events ($n = 3$) and others ($n = 3$). In the non-CR30 group ($N = 63$, after excluding those who died before 30 months), 19 died, with progression being the most frequent cause of death (84%). The 10-year OS was 53% and 87% for non-CR30 and CR30 patients, respectively ($P < 0{\cdot}001$, Fig 3A).

The impact of the main variables on OS of CR30 patients is shown in Table III. Older age, as well as poor performance status (ECOG >1), extranodal involvement, high serum β2 m and high risk FLIPI (Fig 4A) before treatment predicted poorer OS in this group. In addition, patients who reached CR during the maintenance period had worse OS than those reaching CR after induction (Fig 4B). Finally, PET/CT scan after induction (Fig 4C) or maintenance with rituximab (Fig 4D) did not significantly influence OS. A multivariate analysis was performed in this cohort of CR30 patients, including FLIPI score (low plus intermediate *versus* high risk), serum β2 m (normal *versus* high), response after induction treatment as evaluated by CT scan (PR *versus* CR), and maintenance with rituximab (no *versus* yes) as prognostic variables. In the final model with 167 patients, FLIPI was the only independent variable for OS [hazard ratio (HR): 6·45; $P = 0{\cdot}034$]. The results of the univariate and multivariate analysis of CR30 patients from the training series for PFS and OS are shown in Tables I and SII.

We then compared the survival rate of CR30 patients with that of a sex- and age-matched Spanish general population. The 10-year RS was 100%, with no significant decrease in life expectancy with current follow-up (Table IV). The impacts of the main variables on the RS of CR30 patients are listed in Table III. High serum β2 m and high risk FLIPI predicted poorer RS, whereas patients in PR after induction had a trend for shorter RS. Finally, RS of CR30 and non-CR30 cohorts were compared, as shown in Table IV. The decrease in life expectancy at 10 years was 27% and 0% for non-CR30 and CR30 patients, respectively (HR: 5·95; $P < 0{\cdot}00001$) (Fig 3A).

Validation cohort

The main results of the training series were validated in an independent series of 693 patients from the GELTAMO group. Main initial features, PFS and OS, are shown in Fig 1 and Table I. After induction therapy, 525 (76%) patients achieved CR/CRu, 145 (21%) PR and 23 (3%) showed failure to treatment. One hundred and sixty-three of the patients (28%) received maintenance with rituximab. After a median follow-up of 6·7 years (range: 0·7–13·9 years) for surviving patients, 230 patients (33%) relapsed with a 5- and 10-year PFS of 64% (95% CI: 60–68%) and 50% (95% CI:

Table II. Initial characteristics and treatment from training cohort according to disease status at 30 months.

Characteristics	CR at 30 months (n = 188)	P value
Age		
≤60 years	98/144 (68%)	NS
>60 years	90/119 (76%)	
Sex		
Female	107/142 (75%)	NS
Male	81/121 (70%)	
Histological grade		
Grade 1/2	135/187 (72%)	NS
Grade 3a	31/48 (65%)	
B symptoms		
No	166/228 (73%)	NS
Yes	22/35 (69%)	
ECOG performance score		
<1	177/246 (72%)	NS
≥1	11/16 (69%)	
Bulky disease		
No	149/200 (75%)	0·04
Yes	39/63 (62%)	
Stage disease		
I–II	52/62 (84%)	0·009
III–IV	136/201 (68%)	
Extranodal involvement		
No	75/92 (82%)	0·015
Yes	113/171 (66%)	
Bone marrow involvement		
No	99/124 (80%)	0·003
Yes	89/139 (64%)	
Peripheral blood involvement		
No	164/220 (75%)	NS
Yes	17/28 (61%)	
Serum LDH		
Normal	140/188 (74%)	NS
High	41/59 (69%)	
Serum β2 m		
Normal	88/109 (81%)	0·016
High	83/123 (67%)	
FLIPI		
Low risk	59/68 (87%)	0·012
Intermediate risk	63/95 (66%)	
High risk	62/86 (72%)	
Treatment		
R-CHOP/R-FCM	131/187 (71%)	NS
R-CVP	26/34 (76%)	
Others	29/42 (69%)	
Response to induction		
CR/CRu	167/210 (80%)	<0·001
PR	21/44 (48%)	
Response (assessed by PET/CT)		
Complete metabolic response	100/116 (82%)	<0·001
No complete metabolic response	25/42 (60%)	
Maintenance with rituximab		
No	112/174 (69%)	<0·001
Yes	75/88 (87%)	

β2 m, β2-microglobulin; CR, complete response; CRu complete response unconfirmed; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone); R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-FCM, rituximab, fludarabine, cyclophosphamide and mitoxantrone.

45–55%), respectively. During the follow-up, 143 patients died with a 5- and 10-year OS of 84% (95% CI: 82–86%) and 73% (95% CI: 69–77%), respectively. Four hundred and twenty-seven patients (62%) were in CR at 30 months. Ten year OS of CR30 patients was 90% (95% CI: 86–94%; Fig 3B). Variables predicting poor OS among CR30 patients were high serum β2 m, high-risk FLIPI, PR after induction and not receiving maintenance with rituximab (Table SI). A multivariate analysis was performed in these CR30 patients, including FLIPI score (low plus intermediate *versus* high risk), serum β2 m (normal *versus* high) and maintenance with rituximab (no *versus* yes) as prognostic variables. Response after induction treatment was not included in the model because a centralized review of imaging was not carried out in this cohort. In the final model with 317 patients, FLIPI (HR: 3·4; P = 0·025) and serum β2 m (HR: 2·33; P = 0·017) were independent prognostic variables for OS. Thus, FLIPI was validated as prognostic variable in CR30 patients. Univariate and multivariate analysis of both series are shown in Tables SI and SII.

Finally, for the training cohort, we compared the OS of CR30 patients and non-CR30 patients to that of a sex- and age-matched Spanish population. The 10-year RS were 100% and 59% with a decrease in life expectancy of 0% and 41%, respectively (Table IV, Fig 3B).

Analysis of other end points described in the literature

Different end points with diverse time points have been reported in the literature (Casulo *et al*, 2015; Maurer *et al*, 2016; Provencio *et al*, 2017b); OS according to progression of disease (POD) at 12 (POD12), 24 (POD24) and 30 (POD30) months and different statistical methods is depicted in Figure S1.

Discussion

Patients with FL needing therapy have a very long median OS with current treatments, largely based on immunochemotherapy. However, FL remains incurable in

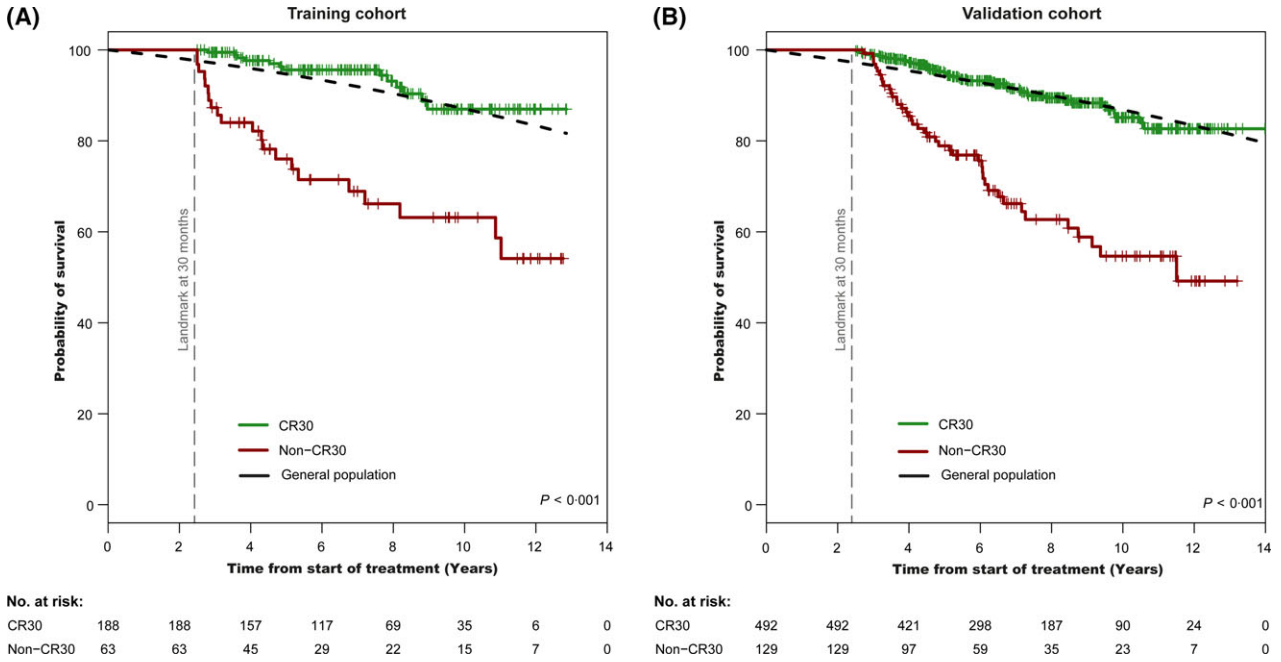

Fig 3. Overall survival according to the status at 30 months in training (A) and validation (B) cohorts. CR30, complete response at 30 months; Non-CR30, no complete response at 30 months.

most cases, with repeated relapses over time. As suggested in the pre-rituximab era and confirmed in recent series, the group of patients who experience early progression of the disease show poor outcomes in terms of OS (Montoto *et al*, 2002; Casulo *et al*, 2015; Jurinovic *et al*, 2016; Maurer *et al*, 2016). Between 19 and 25% of FL patients treated with immunochemotherapy suffer early treatment failure in different studies (Salles *et al*, 2011; Casulo *et al*, 2015; Jurinovic *et al*, 2016), including 22% in current series, whereas most patients have a durable response. Herein, we have focused on the latter, in order to compare their outcome with that of the normal population and assess the prognostic factors specifically in a good prognosis population. We have therefore shown that CR30 patients have a life expectancy that is almost identical to that of a sex- and age-matched Spanish general population and this finding has been validated in an independent cohort. Although this is the first study to our knowledge demonstrating a favourable outcome in terms of relative survival of CR30 patients, these data are not surprising, given that other recent reports have shown the same good evolution of prolonged responders (Provencio *et al*, 2017b). In this sense, the most remarkable finding probably is not the difference in survival between early failures and maintained responders, but rather the huge magnitude of this difference. Only two studies have previously studied the RS of long responders patients (Maurer *et al*, 2016; Provencio *et al*, 2017b). Both studies observed that those patients who achieve event-free survival at 12 or 24 months have a risk of dying similar to the general population. However, we believe that our study has some advantages over those previously mentioned. Our training series is a homogeneous, well-characterized series that includes patients treated only in the rituximab era following our institutional guidelines. Moreover, our series includes PET/CT scan information, which has allowed us to analyse better the characteristics of CR30 patient at diagnosis. Finally, the possible advantages of CR30 instead of POD24 are discussed below.

A limitation of the present study, like that of all studies in the rituximab era, is that the follow-up is necessarily short, consequently limiting the conclusions made in the long term. Therefore, the almost normal life expectancy at 10 years for patients in CR30 does not exclude that life expectancy could be lower at 20 or 30 years. However, we have preferred to include only patients treated in the rituximab era, because rituximab has substantially changed the natural history of the disease, increasing the OS of FL patients. Our study included patients treated with different regimens (R-CHOP/R-CVP and R-FCM), however, these regimen have shown the same efficacy although with different toxicity profiles (Luminari *et al*, 2018).

The use of PFS (or OS) as the primary end-point in clinical trials is a challenge for a disease whose median PFS is curretnly about 6–8 years and median OS close to 20 years (Salles *et al*, 2011; Nastoupil *et al*, 2015; Provencio *et al*, 2017a). For this reason, response to initial therapy assessed at a certain time point has been recently analysed as a surrogate marker for PFS within the setting of clinical trials (Shi *et al*, 2017). The study of individual patient data from 13 randomized multicentre trials of induction and maintenance regimens in first-line FL therapy demonstrated the value of CR30 as a surrogate end-point for PFS. Other reports selected different cut-offs, including 24 months from start of

Table III. Univariate analysis for overall survival in CR30 patients of the training cohort.

Characteristics	10-year OS %; *P* value		10-year RS %; *P* value	
All CR30 patients	87		100	
Age				
≤60 years	93	0·001	100	NS
>60 years	69		99	
Sex				
Female	87	NS	99	NS
Male	88		99	
ECOG performance score				
<1	90	0·002	97	NS
≥1	45		83	
Extranodal involvement				
No	97	0·03	100	NS
Yes	78		93	
Serum β2 m				
Normal	96	0·005	100	0·03
High	72		90	
FLIPI				
Low risk	98	0·001	100	0·043
Intermediate risk	93		100	
High risk	66		88	
Response to induction				
CR/CRu	89	0·04	98	0·09
PR	67		85	
PET/CT scan after induction treatment				
Complete metabolic response	91	NS	100	NS
No complete metabolic response	86		97	
Maintenance with rituximab				
Yes	87	NS	97	NS
No	81		89	

β2 m, β2-microglobulin; CR, complete response; CR30, complete response at 30 months; CRu complete response unconfirmed; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; NS, not significant; OS, overall survival; PET/CT scan, fluorodeoxyglucose-positron emission tomography/computed tomography; PR, partial response; RS, relative survival.

therapy in the so-call POD24 (Casulo *et al*, 2015; Jurinovic *et al*, 2016). In the present study, we primarily selected CR30 as the predictor of outcome due to the preliminary data of the FLASH study (Shi *et al*, 2017), as well as CR30 having additional advantages. First, 30 months corresponds approximately to the duration of the induction therapy plus the 24 months of rituximab maintenance. Moreover, in clinical practice, the re-assessment of response is usually performed at the end of the maintenance period, unless relapse is suspected. Therefore, patients not included in clinical trials having detailed information on status at 30 months are much more realistic than at 24 months.

Our CR30 definition included patients reaching CR with the induction therapy, as well as those in PR who achieved CR during the maintenance period. It is well known that about 30–50% of PR patients eventually reach CR during the maintenance period (Salles *et al*, 2011), and this figure was 48% in our series. Although the prognosis of the latter is considered good, our data suggest that the outcome of converted patients is somewhat worse in terms of survival. Other variables predicting survival in the subset of CR30 patients were FLIPI and β2 m at diagnosis. The FLIPI score is a validated tool to stratify FL patients into risk groups and predict prognosis by incorporating clinical and laboratory features upon diagnosis of the disease (Solal-Céligny *et al*, 2004). However, FLIPI is not routinely used to guide risk-adapted treatment strategies. We found that high-risk FLIPI score predicted poorer OS in CR30 patients. These findings suggest that FLIPI also remains an important prognostic factor during the evolution of patients. Finally, PET/CT imaging has been recommended for the evaluation of response after induction therapy in FL (Cheson *et al*, 2014) and several studies (Pyo *et al*, 2013; Trotman *et al*, 2014) have shown to be a good predictor of PFS and OS in these patients. For this reason, we also evaluated the impact of response assessed by PET/CT scan after induction in about 60% of patients in whom this exploration was available. Interestingly, within the subset of CR30 patients, we observed no significant impact on survival prediction. Of course, it may be argued that the series was not powerful to detect differences due to the relatively low number of patients with favourable prognosis.

A recently published study (Pastore *et al*, 2015) showed that integration of the mutational status of seven genes with clinical risk factors (m7-FLIPI) improves prognostication for patients with FL receiving first-line immunochemotherapy. This score has emerged as a promising approach to identifying the subset of risk. In this sense, Jurinovic *et al* (2016) evaluated the ability of pre-treatment risk models to predictive early treatment failure and observed that m7-FLIPI was highly accurate in predicting POD24. These findings suggest that long responders could have a particular biological profile. Therefore, future studies should be directed towards studying the biological profile of this group of patients with FL with good prognosis in order to allow for guidance on risk-adapted treatment strategies.

New effective treatment approaches are currently available for patients with FL particularly at relapse/progression. However, these drugs show non-negligible toxicities, such as infections, drug-induced pneumonitis, diarrhoea/colitis, neutropenia or infusion-related reaction. (Radford *et al*, 2013; Coutré *et al*, 2015; Salles *et al*, 2017) Although CR30 patients may relapse in the future, these patients have an excellent outcome with standard therapeutic approaches and, therefore, are not the best candidates for potentially toxic investigational regimens.

In conclusion, FL patients treated with immunochemotherapy who were in CR at 30 months from the start of the treatment show similar survival rate to that of a sex- and

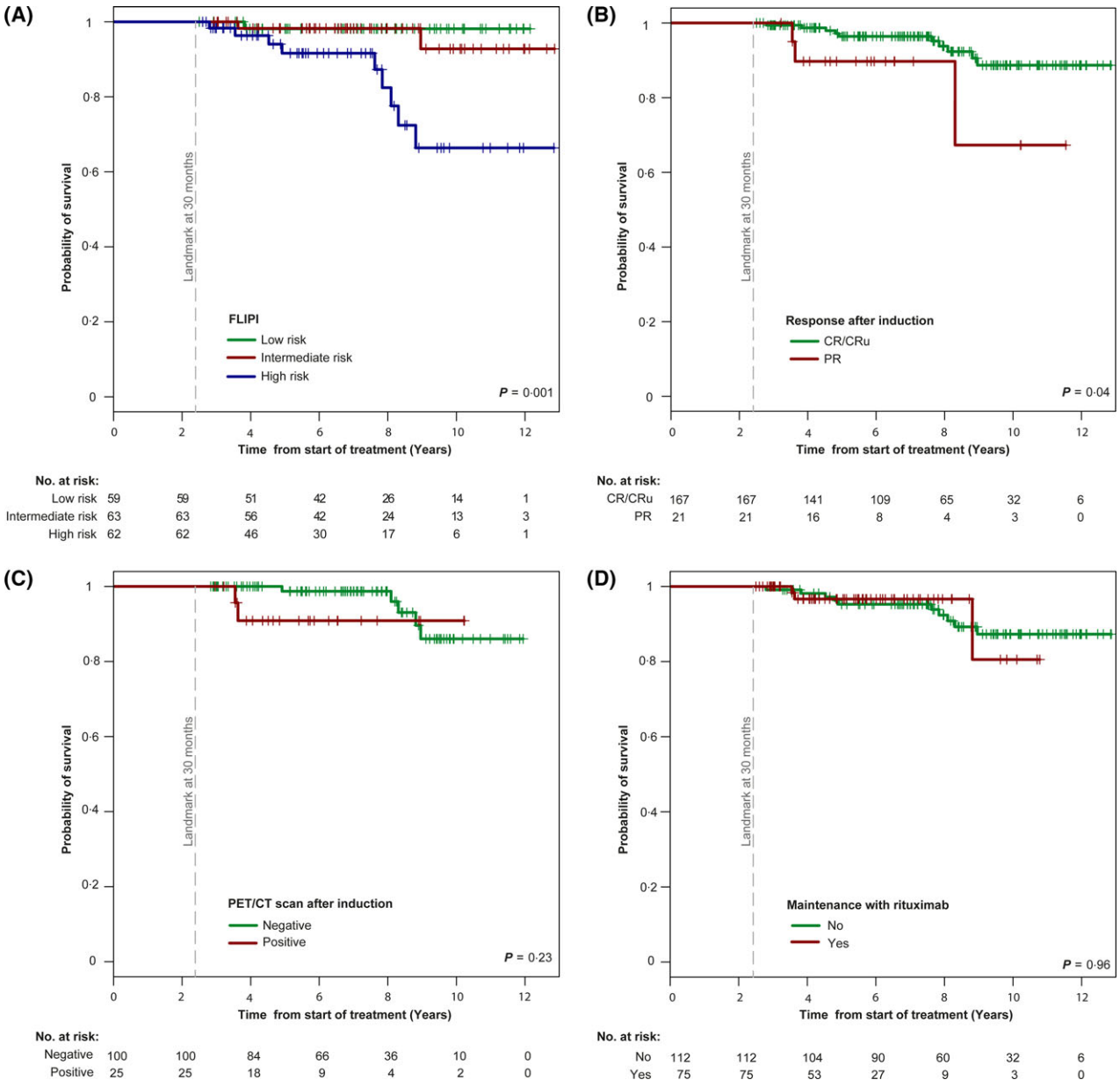

Fig 4. Overall survival of CR30 patients according to FLIPI score (A), response after induction (B), PET/CT scan after induction (C) and maintenance with rituximab (D). CR, complete response; CRu, complete response unconfirmed; FLIPI, Follicular Lymphoma International Prognostic Index; PET/CT scan, fluorodeoxyglucose-positron emission tomography/computed tomography; PR, partial response.

Table IV. Overall survival and relative survival of CR30 and non-CR30 patients in training and validation cohorts.

	Training cohort (n = 251)		Validation cohort (n = 623)	
	n	10-year RS (95% CI)	n	10-year RS (95% CI)
CR at 30 months	188	100% (94–100%)	427	100% (95–100%)
No CR at 30 months	63	73% (57–88%)	196	59% (47–71%)
		P < 0·0001		P < 0·0001

CI, confidence interval; CR, complete response; RS, relative survival.

Patients who died before the land-mark (30 months) are not included in this table.

age-matched Spanish general population. CR30 can be therefore considered a strong predictor of OS in FL patients.

Funding source

This work was supported by PI16/00420 (to EG and ALG), PMP15/00007, PIE13/00033 (to ALG), Instituto de Salud Carlos III, Ministerio de Salud, España, SAF12-38432, Ministerio de Economía y Competitividad, CIBERONC, GEL-LFT-2014-01 (from GELTAMO group), and the program "Fellowship de Gilead Sciences" to ALG and PERIS SLT002/16/00374. A. Rivas-Delgado was supported by a "Josep Font" grant (Hospital Clinic de Barcelona).

Authorship contributions

Conception and design: AL-G, LM, MDC, SA, MA.
Provision of study materials or patients: LM, SA, MA, ARD, AM, FN, MA, MEL, GR, JMS, MM, SM, IC, AS, FGP, RA, JC, MJT, AIT, AJ-U, AR, AGV, JLB, LL, SN, EC, MEI, EP, SM, MG, AM.
Data analysis and interpretation: ALG, LM.
Manuscript writing: LM, AL-G.
Study supervision: AL-G, MDC.
Final approval of manuscript: All authors.

Disclosure of conflicts of interest

The authors declare no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Results of the univariate analysis of CR30 patients from the training and validation series for PFS and OS.

Table SII. Results of the multivariate analysis of CR30 patients from the training and validation series for PFS and OS.

Figure S1. OS according to POD12, POD24 and POD30 and different statistical methods.

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